flanking sequences from huntingtin. Also, we show that electrostatic repulsions due to these residues retard the rate of monomer loss and large, linear, ordered clusters are formed. Our observations provide a unifying framework, capturing all known features of the early stages of aggregation in polyglutamine containing systems.

1992-Pos Board B11

A Class of Self-Assembling Aliphatic Ultrasmall Peptides as a Model System for Understanding and Preventing Amyloidosis

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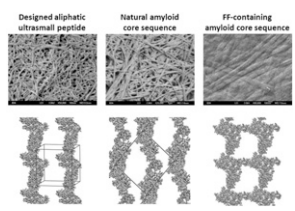
Core sequences of 4-7 residues that form amyloid fibrils have been identified within natural amyloid proteins. However, the mechanism of amyloid aggregation remains unclear. We designed a new class of aliphatic peptides (with 3-6 residues) that self-assemble in water to amyloid β-type fibers via α-helical intermediates. We compared the self-assembly of our designed peptides with core sequences in Amyloid-beta, Amylin and Calcitonin using a multimodal approach. A common feature was the appearance of α-helical intermediates before the final β-turn structures. Another amyloid-beta core sequence containing the diphenylalanine motif was chosen to evaluate the role of aromatic residues in self-assembly. The repeated occurrence of aromatic residues in core sequences has led to widespread conclusions about their key role in driving self-assembly. Surprisingly, the diphenylalanine-containing sequence did not form cross-β aggregates or involve the α-helical intermediate step. Our study puts forth a new, simplified model system to study amyloidosis and indicates that aromatic interactions are not as important as previously postulated. The results provide valuable insight into the early intermediates and factors driving self-assembly, which is necessary for developing small molecule therapeutic drugs that prevent amyloidosis.



1993-Pos Board B12

Discrete Molecular Dynamics Study of Oligomer Formation by N-Terminally Truncated Amyloid B-Protein

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Alzheimer's disease (AD) is strongly linked to amyloid b-protein (Ab). Two predominant alloforms, Ab1−40 and in particular Ab1−42, are known to form toxic oligomers. The N-terminally truncated, pyroglutamated forms of Ab1−40 and Ab1−42 are highly resistant to peptidase degradation and can seed Aβ aggregation. Discrete molecular dynamics (DMD) simulations previously captured in vitro derived distinct Ab1−40 and Ab1−42 oligomer size distributions and predicted that the more toxic Ab1−42 oligomers had more flexible and solvent exposed N-termini than Ab1−40 oligomers. Here, oligomer formation by four N-terminally truncated Ab peptides: Ab3−40, Ab3−42, Ab11−40, and Ab11−42 was examined by the DMD approach. In our simulations, the four N-terminally truncated peptides showed increased oligomerization propensity, consistent with their in vitro tendency to seed aggregation. Conformations formed by Ab11−40 had the lowest b-strand and the highest turn content. The tertiary and quaternary structure of Ab3−4X oligomers was distinctly different from that of Ab11−4X oligomers. Ab3−4X oligomers were characterized by more disordered and solvent exposed N-termini than oligomers formed by the full-length peptides. In contrast, in comparison to Ab1−4X, Ab11−4X oligomers had a more compact structure, facilitated by Val12, resulting in less flexible and less solvent exposed N-termini, suggesting reduced Ab11−4X-mediated toxicity. This unique behavior of the N-termini in Ab peptides might provide a plausible explanation for the experimentally observed increased toxicity of Ab3−4X peptides and their pyroglutamated forms.

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Intrinsic Disorder and Chaperon-Like Activity of Different Caseins

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Casein is the best characterized milk protein and constitutes over 70-80% of total bovine milk protein. In milk, casein exists as large micelle-like particles that comprise four unrelated proteins (αs1-, αs2-, β-, and κ-casein) and calcium phosphate. Although αs1-, αs2-, β-, and κ-casein present important structural differences, all of them adopt extremely open and flexible conformations, enough to be defined intrinsically disordered proteins (IDPs). Caseins are able to inhibiting protein aggregation and amyloid fibrils formation and this chaperon-like activity could be largely due to their structural disorder. In the present study we discuss the meaning of ''disorder'' in the case of three caseins α, β and k that have similar unordered structure and different sequence. We correlate the different type and disorder degree to the capability of preventing protein aggregation and amyloid formation. The physical-chemical parameters of α, β and k caseins were compared to those of intrinsically unfolded and ideally globular proteins. Moreover, caseins sequences were analyzed by several publicly available disorder-oriented predictors two metaservers, MeDor and meta-PRDOS, and by a neural network algorithm (PONDR). We observed that α, β and k caseins have different degree and type of disorder, depending on the parameters under analysis and criteria used by the different predictors. These data were correlated to experimental results (ThT fluorescence, CD) on the caseins effect on 1-40 β-amyloid peptide fibrillogenesis. Experiments showed that k-casein forms ordered aggregates and that it is able to significantly increase lag-time and reduce fibril amount in Aβ amyloid formation. Our results contribute to clear the role of intrinsically disordered proteins and their mechanism of action by functional order/disorder transitions, and offer insight in the field of prevention and therapy in Alzheimer diseases, and, in general, of amyloid pathologies.

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Cellular Polyamines Promote Amyloid-Beta Peptide Fibrillation and Modulate the Aggregation Pathways

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The cellular polyamines spermine, spermidine, and their metabolic precursor putrescine, have long been associated with cell-growth, tumor-related gene regulations, and Alzheimer's disease. Here, we show by in-vitro spectroscopy and AFM imaging, that these molecules promote aggregation of amyloid-beta (Aβ) peptides into fibrils and modulate the aggregation pathways. NMR measurements showed that the three polyamines share a similar binding mode to monomeric Aβ(1-40) peptide. Kinetic ThT studies showed that already very low polyamine concentrations promote amyloid formation: addition of 10 μM spermine (normal intracellular concentration is ~1 mM) significantly decreased the lag and transition times of the aggregation process. Spermidine and putrescine additions yielded similar but weaker effects. CD measurements demonstrated that the three polyamines induce different aggregation pathways, involving different forms of induced secondary structure. This is supported by AFM images showing that the three polyamines induce Aβ(1-40) aggregates with different morphologies. The results reinforce the notion that modulation of the Aβ peptide aggregation pathways towards minimally toxic ones by addition of suitable ligands may be a possible therapeutic strategy for Alzheimer's disease.

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Cyclic N Terminal Fragment of Amylin Forms Non Amyloid Fibers: Implications for Intra- and Inter-Molecular Interactions in Amylin

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Islet amyloid polypeptide (IAPP), also known as amylin, is a 37-residue intrinsically disordered hormone peptide that is secreted together with insulin by the beta cells of the pancreas, and is involved in glucose regulation and gastric emptying. IAPP is implicated in the pathogenesis of diabetes type II, due to its deposition in the form of amyloid fibers in the beta cells of the pancreas, where insulin is produced. IAPP contains a highly conserved, functional disulfide bond that confers a short ring-like structure (N_loop) to the N-terminus of the peptide. Removal of this functional element alters both the mass per length distributions of hIAPP fibers and the kinetics of fibril formation. The mechanism by which the N_loop affects hIAPP aggregation is not yet understood,